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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/525,361 | 03/15/2000 | David Mack | A-67860-3/RMS/DAV | 9370 |

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| EXAMINER | |
|---|---|
| JOHANNSEN, DIANA B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 08/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/525,361 | MACK ET AL. | |
| | Examiner | Art Unit | |
| | Diana B. Johannsen | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *48,49,52 and 54-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48,49,52 and 54-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**FINAL REJECTION**

1. This action is in response to the Amendment and Response filed May 8, 2003. Claims 48-49, 52, and 55-58 have been amended and claims 50-51 and 53 have been canceled. Claims 48-49, 52, and 54-58 are now pending and under consideration. The amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Priority***

3. Regarding priority, it is noted that the Response states that "the claims currently under examination, which are drawn to SEQ ID NO: 23, are supported in the priority application US Application No. 09/450,810, filed November 29, 1999." The response states that "Support in the priority application can be found, e.g., on the second to the last page of Figure 8, 5$^{th}$ entry from the bottom, which shows that a sequence corresponding to the accession number W72838 is overexpressed in breast cancer compared to normal," and that "This accession number is also set forth in Figure 10, first entry on page 14, of the instant application which further discloses that this accession number corresponds to BCH1 (see also, e.g., Figure 12, first entry)."

Applicants' arguments have been thoroughly considered but are not persuasive. First, it is noted that while the '810 application does disclose an accession no. "W72838," the sequence of SEQ ID NO: 23 is not actually recited in the '810

application. Sequences corresponding to particular accession numbers are not fixed and definite but rather change over time (for example, whenever sequence errors are discovered and corrected), and Applicant has not provided, e.g., declaratory evidence that the sequence recited in SEQ ID NO: 23 is in fact identical to the sequence that corresponded to accession no. W72838 at the time the '810 application was filed. Second, regarding the '810 application data cited by Applicants as supporting the instant application, it is noted that even if it is established that the "W72838" sequence of Table 8 of the '810 application is identical to instant SEQ ID NO: 23, the '810 disclosure does not provide support for the invention of the instant claims. The claims are drawn to a method in which increased expression "relative to normal breast tissue" is indicative of cancer. However, Table 8 of the '810 application indicates that the ratio of expression of W72838 in breast tumor tissue compared to normal breast tissue is "1.0" (i.e., that there is no difference in expression of this sequence in tumor tissue as compared to normal tissue). Accordingly, Applicants' argument is not persuasive. The effective filing date of the instant application remains March 15, 2000.

***Specification***

4. The amendment filed October 16, 2001 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows. Applicant amended the description of Figure 10 to recite SEQ ID Nos 54, 56, 57, 59, 60, and 61, and concurrently amended the Sequence Listing to add sequences corresponding to

these SEQ ID Nos. The new Sequence Listing added by Applicant also includes new SEQ ID Nos 55, 58, and 62, which appear to constitute polypeptides encoded by SEQ ID Nos 54, 57, and 61, respectively. SEQ ID Nos 54-62 were not disclosed in the instant application as filed. It is noted that the sequences added by Applicants' amendment correspond to particular Accession Nos. that were disclosed in Figure 10. However, the Figure does not recite the sequences, and Applicant has not provided, e.g., declaratory evidence that the sequences added to the specification constitute the particular sequences that corresponded to these accession numbers at the time the invention was made. Accordingly, Applicants' amendment introduces new matter into the specification. Applicant is required to cancel the new matter in the reply to this Office Action.

It is noted that Applicant's response states that, upon the identification of allowable claims, "Applicants will cancel the matter in question or provide the required declaratory evidence." As Applicant has yet to cancel the new matter or provide the required declaratory evidence, this objection is maintained.

***Claim Rejections - 35 USC § 112***

5. In view of the cancellation of claims 50-51 and 53, the rejection of the claims under 35 U.S.C. 112, first paragraph, is moot.

6. Claims 48-59, 52, and 54-58 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth below and in the Office action of December 4, 2002.

It is noted that Applicants have overcome the instant rejection in part by amending the claims to require a sample "comprising breast tissue," to require that "the

polynucleotide is an mRNA," and to require that "an increase in the level of the polynucleotide relative to normal breast tissue is indicative of cancer." However, the claims as amended still encompass non-human patients, and claims 48, 52, and 55-57 as amended still encompass the detection of polynucleotides that encode amino acid sequences other than SEQ ID NO: 25.

Regarding "non-human patients," the response does not traverse the rejection. Regarding polynucleotides encoding amino acid sequences other than SEQ ID NO: 25, the response traverses the rejection on the following grounds. The response argues that "The current invention involves detecting overexpression of the mRNA as recited in the claims in breast cancer in comparison to normal breast tissue" and that "The specification teaches how to perform such an analysis (*see, e.g.*, page 42, lines 9-24)." The response states that "Applicants present data showing that BCH1 mRNA sequences are overexpressed in individual breast tumor samples relative to normal (*see, e.g.*, Figures 36 and 38 and the "Examples" section)." The response further urges that the claims "are drawn to nucleic acid sequences having at least 95% identity to the reference sequence" and that "Such sequences are even more closely related on the polypeptide sequence level." The response states that "this recitation covers sequences such as allelic variants" and argues that "one of skill could reasonably predict that such closely related variants would also be diagnostic of breast cancer in individual patient samples."

Applicants' arguments have been thoroughly considered but are not persuasive. It is acknowledged that it is well within the ability of one of skill in the art to analyze

expression of mRNA, including overexpression of mRNA that occurs in breast cancer tissue as compared to normal breast tissue. However, in order for such methods to be useful in achieving cancer diagnosis, an association between breast cancer and overexpression of the mRNA detected must exist. In the instant case, as discussed in the Office action of December 4, 2002, the teachings of the specification and of the prior art provide evidence that overexpression of SEQ ID NO: 25 is associated with breast cancer and with poor cancer prognosis. However, the large majority of the mRNA molecules encompassed by the claims as written encode amino acid sequences other than SEQ ID NO: 25. As neither the prior art nor the specification provide any evidence of an association between expression of such other molecules and breast cancer, it is completely unpredictable as to whether such a relationship exists. Regarding Applicants' arguments that the claims encompass allelic variants, it is noted that the claims are not limited to such variants, and further that such variants, alone or in combination with molecules encoding SEQ ID No: 25, are not representative of the large genus claimed. Further, no evidence of record indicates that increased expression of any allelic variant of SEQ ID NO: 25 is associated with breast cancer. Accordingly, Applicants' arguments are not persuasive, and this rejection is maintained.

***Claim Rejections - 35 USC § 103***

7. In view of the cancellation of claims 50-51 and 53, the rejection of those claims under 35 U.S.C. 103(a) as being unpatentable over Reed et al (WO 99/33869 A2 [7/1999]) in view of Khan et al (Electrophoresis 20:223-229 [2/1999]) is moot.

8. Claims 48-49, 52, and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al (WO 99/33869 A2 [7/1999]) in view of Khan et al (Electrophoresis 20:223-229 [2/1999]), for the reasons set forth in the Office action of December 4, 2002.

The response traverses the rejection on the following grounds. The response argues that Reed et al's sequence was identified in a subtraction library constructed by performing subtractive hybridization with cDNA libraries prepared from pooled patient samples and normal samples. The response argues that while Reed et al state that "twenty one distinct cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested," it "is not clear how this analysis was performed." The response continues that "The only description of how the sequence at issue was 'determined' to be over-expressed in breast tumors is that it is from the breast tumor subtraction library." The response urges that "There is no disclosure that the sequences were confirmed to be overexpressed in individual breast tumor samples," that "there is no description or confirmation of overexpression of this sequence in any tissue or cell other than in the library," and that "in the absence of confirming studies" one of skill in the art would not conclude that Reed et al's sequence could be used diagnostically with a reasonable expectation of success.

Applicants' arguments have been thoroughly considered but are not persuasive for the following reasons. First, Reed et al's statement that clones (including SEQ ID NO: 56) "were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested" is recited in a portion of the specification describing

subsequent analysis of one subset of clones initially identified by subtractive hybridization (see pages 29-30 of Reed et al). Accordingly, Reed et al's disclosure regarding SEQ ID NO: 56 is not limited to, e.g., a teaching that this sequence was merely a member of the prepared subtraction library: the statement that a subset of clones including SEQ ID NO: 56 "were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested" indicates that further determination of the expression level of SEQ ID NO: 56 in at least some breast tumor and normal tissues did occur. While it is acknowledged that Reed et al do not provide, e.g., specific results obtained with various individual tumor and normal tissue samples, it is noted that Applicant's specification in fact provides no data regarding mRNA levels in such samples. While Applicants' specification states at page 63 that "Expression studies were performed herein on both the protein and nucleic acid levels," the data reported in the specification is limited to protein levels (see pages 63-64). It is well-known to those of skill of the art that variations in protein levels may arise for reasons other than altered mRNA levels, and, as discussed in the Office action of December 4, 2002, it is the data of Reed et al that provides evidence of an alteration in mRNA corresponding to the elevated protein levels reported by Applicants, thereby enabling the methods of the claims, which require polynucleotide (rather than polypeptide) detection. Accordingly, Applicants' arguments are not persuasive.

The combined references of Reed et al and Kahn et al suggest all the limitations of present claims 48-49, 52, and 55-57, and therefore this rejection is maintained.

9. In view of the cancellation of claims 50-51 and 53, the rejection of those claims as being unpatentable over Reed et al (WO 99/33869 A2 [7/1999]) in view of Hackl et al (Anticancer Research 18(2A):839-842 [March-April, 1998]) is moot.

10. Claims 48-49 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al in view of Hackl et al, for the reasons set forth in the Office action of December 4, 2002.

The response traverses the rejection on the grounds that the Hackl et al reference "does not cure the defects noted above in Reed et al." This argument has been thoroughly considered but is not persuasive. Regarding the Reed et al reference, the response to Applicants' arguments set forth in paragraph 8, above, applies equally herein. Further, it is noted that the Hackl et al reference was not cited to "cure" the supposed defects in Reed et al asserted by Applicants, but for its teaching that RT-PCR may be used to semiquantitatively determine levels of estrogen receptor (ER) and progesterone receptor (PgR) mRNA in breast tumor tissue samples obtained from patients, and that mRNA detection is more sensitive than methods of detecting protein and allows detection of ER and PgR mRNA in some instances when protein is not detected, as discussed in the Office action of December 4, 2002.

The combined references of Reed et al and Hackl et al suggest all the limitations of present claims 48-49 and 52, and therefore this rejection is maintained.

***Conclusion***

**11. THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B Johannsen

CARLA J. MYERS
PRIMARY EXAMINER

Diana B. Johannsen
August 19, 2003